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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,019	HARRIS ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *24,46 and 56-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23, 25-45, 47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/4/02; 9/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Alignments 1-3*.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-23, 25-45 and 47-55, in the reply filed on 1/24/2005 is acknowledged.

The traversal is on the ground(s) that searching all of the claims would not prove unduly burdensome.

This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. As stated in the MPEP § 803, "a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02." These criteria were met in the above restriction. Each of the three Groups in the restriction requirement is classified in a separate class and subclass. Thus, the groups require divergent searches, and to search all inventions would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Claims 24, 46, 56-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-23, 25-45 and 47-55 are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/18/2002 has been considered by the examiner. However, since the PCT Search Report cited therein is not true publication with a publication date, it is not fully in compliance with 37 CFR 1.97 and will not be printed on the face of the patent issuing from this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23, 25-45 and 47-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for high level expression of a RAGE protein wherein the method comprises (a) a soluble RAGE protein encoded by SEQ ID NO: 1 or 2; (b) a suspension culture; and (c) the following parameters: sf9 or sf21 cells, *Autographa californica* virus, a rate of cell growth of 18-26 hours, and a cell viability of greater than 90%; or (2) an insect cell producing a soluble RAGE protein encoded by SEQ ID NO: 1 or 2, does not reasonably provide enablement for (1) method of high level expression RAGE, wherein the method comprises (a) other RAGE proteins, including a membrane bound RAGE of SEQ ID NO: 1; (b) a non-suspension culture such as a monolayer culture; or (c) parameters differing from those aforementioned; or (2) an insect cell producing a soluble RAGE protein other than the protein encoded by SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With respect to the RAGE protein produced in the method of claims 1-11, 15-22, 25-29, 33-44, and 47-51, the claims encompass variants and fragments of any RAGE protein in which one or more amino acids are substituted, deleted, and/or inserted. Claims 12-14, 30-32, and 52-54 recite specific SEQ ID NOs 1, 2, or 4 but also encompass "a sequence substantially homologous thereto". This phrase "substantially homologous" is defined in the specification on page 12 as encompassing any two amino acid sequences which when aligned are at least 75% homologous.

The nucleic acids of SEQ ID NO: 1 and 2 encode the membrane and soluble form of the RAGE polypeptide. These polypeptides have been shown to have various useful characteristics, such as binding amphoterin (see Hori et al, 1995. Journal of

Biological Chemistry. 270: 25752-25761; cited by the Applicants as reference 38 on the IDS submitted 9/4/2002) or, in the case of the soluble form, treating symptoms of diabetes (see Stern et al. U.S. Patent No. 6,790,443). However, insufficient guidance is provided as to which of the myriad of variant encoded polypeptides will retain the characteristics of a RAGE protein of SEQ ID NO: 1 or 2. This includes the polypeptide consisting of the variable (V) domain of RAGE, which is encoded by SEQ ID NO: 4. The specification asserts on page 4 that the V-domain of the RAGE receptor is physiologically active, but has not provided any evidence that it actually retains any of the characteristics of SEQ ID NO: 1 or 2, or actually is physiologically active.

None of the claims include the limitation that the polypeptide variants exhibit characteristics of the parent polypeptide of SEQ ID NO: 1 or 2. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 1 or 2. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 1 or 2, nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 1 or 2 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 1 or 2 and yet still retain the activity of the polypeptide of SEQ ID NO: 1 or 2 - which has apparently not been disclosed.

Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 1 or 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 1 or 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 1 or 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 1 or 2. Conversely, if a protein variant of SEQ ID NO: 1 or 2 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function:

novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

With respect to the insect cells of claims 23, 45, and 55, the claims encompass any polynucleotide encoding a RAGE protein, include variants of SEQ ID NO: 1 or 2. These claims lack enablement for variants of SEQ ID NO: 1 or 2 for the same reasons that the methods of expression of variants of SEQ ID NO: 1 or 2 lack enablement, as described above.

With respect to the type of culture used in the methods, all of the method claims encompass a method using cells grown in suspension in a suspension culture, or cells grown on a solid support, such as a monolayer culture. See specification, page 166, lines 3-5. The only example of a method of high-level expression (Example 2, pages 24-27) uses cells grown in a suspension culture. The relevant art teaches that suspension cultures produce more protein than monolayer cultures (see page 27 of Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999; cited by Applicants as Reference #30 on the IDS submitted 9/4/2002). Furthermore, the method of the invention taught on pages 25-27 of the specification requires that the cell density

of the culture be measured at the initiation of the culture, and at the time of infection. Kretzdorn et al, U.S. Patent No. 6,555,346, published 4/29/2003 teaches (col. 4, lines 6-7) that "it is difficult to establish the cell density in monolayer cultures". Therefore, because Applicants have only taught a method of high level expression using suspension cultures, it is unpredictable whether or not cultures on solid support would produce at least 25, or 50, or 100, or 250 mg/L of protein as claimed. In order to use the invention as claimed one of skill in the art would need to engage in undue experimentation in order to determine whether or not this method would produce this amount of protein in a monolayer culture.

With respect to the parameters of the method of high-level expression of RAGE protein, the specification (Example 2, pg 24-27) teaches a method comprising the following parameters: sf9 or sf21 cells, *Autographa californica* virus, a rate of cell growth of 18-26 hours, and a cell viability of greater than 90%. However, each of the claimed methods encompasses a broader genus of methods with parameters that vary from one or more of the parameters taught in the Example. The specification does not provide any examples of high-level production a RAGE protein wherein the parameters used in the method comprise the following: cells other than sf9 or sf21; a virus other than *Autographa californica*; a rate of cell growth of 18-26 hours; or a cell viability less than 90%. Importantly, the specification does not teach what parameters can be altered and still retain the claimed level of protein production, nor does the specification provide teaching as to what combination of variations will produce the same level of protein expression. The specification does not teach any examples of performing the method with cells other than sf9 or sf21, such as bacterial or mammalian cells or viruses other than *A. californica*. As taught on page 201 of Jarvis et al, 1993 (cited by Applicants as Reference #43 on the IDS submitted 9/4/2002) "low levels of expression in the baculovirus system are often as high as the best expression levels obtained in other eukaryotic systems". Therefore, it is unlikely that other cell hosts or viruses would produce the level of protein expression required by the claims. Furthermore, the Clontech Manual, page 27 teaches "to achieve maximal protein expression, use ... log phase Sf21 cells that are at least 98% viability" and further teaches (page 10) that the

optimum doubling time of Sf21 is 20-24 hours. As the specification only provides examples for >90% viability and cells with a doubling time between 18-26 hours, and the relevant art teaches that maximum protein expression occurs at specific viabilities and doubling times, it is not predictable whether or not that methods with cells less than 90% viability and doubling times outside the range of 18-26 hours would produce the claimed level of protein expression. Because the teachings in the relevant art cast doubt on the predictability of methods with variations in these parameters (outside those taught in the example) to produce the claimed level of protein, to use the claimed methods over the full breadth of the claims, one of ordinary skill in the art would need to engage in undue experimentation in order to determine whether or not each altered parameter would produce the same level of protein expression. Due to the large quantity of experimentation necessary to test each parameter variable recited in the claims to determine whether or not the required level of protein is produced, the lack of direction/guidance presented in the specification regarding which parameters can be altered and still produce the required expression level, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the altering parameters, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-23, 25-45 and 47-55 are rejected, under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1-23, 25-45 and 47-55 are genus claims because the claims are directed to methods of using polynucleotides encoding variant polypeptides, and insect cells comprising said polynucleotides. Each genus is highly variant because a significant number of structural differences between genus members are permitted. For example, claim 13 recites a method of expressing a polypeptide encoded by SEQ ID NO: 2, or a sequence substantially homologous thereto, which encompasses any nucleic acid comprising a nucleic acid with 75% similarity to a SEQ ID NO: 2. The claims do not require that the polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of methods using polynucleotides or insect cells comprising polynucleotides defined only by sequence similarity. However, the instant specification fails to describe the entire genus of methods that are encompassed by each of these claims. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants have possession of and what Applicants are claiming. From the specification, it is clear that Applicants has possession of method of high level expression of a RAGE protein encoded by SEQ ID NO: 2, and an insect cell comprising SEQ ID NO: 2. The claims, however, are not limited to a method of high level of expression a nucleic acid with the specific nucleic acid sequence of SEQ ID NO: 2. The claims only require the claimed polynucleotides to share some structural similarity to the isolated nucleic acid molecule of SEQ ID NO: 2. The specification only describes a method of producing a protein using the nucleic acid sequence of SEQ ID NO: 2 and fails to teach or describe any other nucleic acid which lacks the sequence of SEQ ID NO: 2 and can be used to produce high level of the RAGE protein.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polynucleotides to be used in the claimed methods or cells. There is not even identification of any particular portion of the structure that must be conserved. Therefore the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polynucleotides to be used in the claimed methods or cells. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods or cells comprising a nucleic acid of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "the insect media" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "insect cells" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites "the method of claim 15, wherein the step of infecting cells at a low density comprises cells having an initial density of no more than $0.5x10^6$ cells per

ml." There is insufficient antecedent basis for the limitation of "infecting cells at a low density" in claim 16. In claim 15 the cells appear to be infected at "preset final density" and there is no step of "infecting cells at a low density". In this regard, claim 16 would be rendered definite if amended to read, "...wherein the step of initiating cultures of insect cells at a low density comprises cells having an initial density of no more than $0.5x10^6$ cells per ml."

Claims 9-11 are rejected because they depend from rejected claim 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 45, and 55 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Morser et al, U.S. Patent No. 5,864,018, published 1/26/1999 (cited by the Applicants as Reference #9 on the IDS submitted 9/4/2002).

Claims 23, 45, and 55 encompass insect cells producing recombinant RAGE or a fragment thereof according to the method claim from which they depend. The method claims do not provide any limitations that change the inherent nature of the cells: in each of claims 23, 45, and 55 the claims encompass any insect cell producing recombinant RAGE or a fragment of thereof. The term RAGE is not limited to any particular sequence and encompasses any RAGE or fragment from any species.

Morser et al teaches (column 20, line 40 to column 21, line 27), Sf9 insect cells expressing soluble human RAGE protein. Therefore, Morser clearly anticipates instant claims 23, 45, and 55.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-22, 25-29, and 31-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morser et al, U.S. Patent No. 5,864,018, published 1/26/1999 (cited by the Applicants as Reference #9 on the IDS submitted 9/4/2002) in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002).

The claims are directed to methods of high-level expression of a RAGE protein. Claim 1 is the broadest and the other claims add various limitations to this method, However, each of claims 1-11, 13-22, 25-29, and 31-44 encompass a method with the following steps:

(a) subcloning a nucleotide encoding soluble RAGE into an *Autographa californica* virus;

(b) infecting Sf21 insect cells at an MOI of 0.1;

(c) incubating the insect cell culture at a temperature of 27°C for 5 days to prepare high titer virus stock;

(d) titering the virus to determine MOI;

(e) initiating culture of insect cells at an initial density of about $2.5x10^5$ cells/ml;

(f) growing the insect cells such that the growth rate comprises a doubling time of about 18-26 hours and the cells comprise a viability of greater than 90% until the cell density comprises $1x10^6$ cells/ml;

(g) adding virus from step (d) at a MOI of 5;

(h) incubating the infected culture under conditions of about 26-28 for a predetermined time;

wherein said conditions produced a yield of RAGE polypeptide of more than 250 mg per liter of culture;

Furthermore, all of the claims encompass an additional limitation that the RAGE protein is purified from the media using Sepharose.

Note: The interpretation that all of the claims encompass soluble RAGE is based on the fact the class either recite "RAGE or a fragment" or in the case of claims 13, 14, 30 and 32, the claims recite specific sequences for the RAGE protein (SEQ ID NO: 2 or 4) as well as sequences "substantially homologous thereto". The specification teaches on page 12 that "substantially homologous" refers "to at least two amino acid sequences which when optimally aligned, are at least 75% homologous..." As shown in Sequence Alignments #1-2 (attached to this Office Action), instant SEQ ID NO: 2 is 99.5% similar to Morser SEQ ID NO: 1 and instant SEQ ID NO: 4 is 100% identical to Morser SEQ ID NO: 1. As Morser SEQ ID NO: 1 is soluble RAGE protein, claims 13, 14, 30, and 32 encompass soluble RAGE.

Morser teaches (column 20, line 40 to column 21, line 27) a method of expression of soluble human RAGE in Sf9 insect cells. Morser further teaches purification of the RAGE protein using Sepharose (col 21, line 9) (see claims 7, 29, and 48). Morser does not teach the yield (in mg/L) of sRAGE, and because the details of the method differ from those taught by Applicant, it is unknowable what the yield of the method of Morser is.

The Clontech manual teaches a method of expression comprising the following:

(a) subcloning a nucleotide encoding a protein into an Autograph californica virus (pages 18-23);

(b) infecting Sf21 insect cells at an MOI of 0.1 (page 25, Part D, step 2);

(c) incubating the insect cell culture at temperature of 27°C for 4-6 days to prepare high titer virus stock (page 25; Part D, step 3);

(d) titering the virus to determine MOI (pages 17 and 26);

(e) initiating culture of insect cells at an initial density of about $2x10^5$ cells/ml (page 27, Part XI);

(f) growing the insect cells such that the growth rate comprises is log phase (2-24 hr; page 10) and the cells are at least 98% viable until the cell density comprises $1x10^6$ cells/ml (page 27, Part XI);

(g) adding virus from step (d) at a MOI of 5 or 10 (page 27, part X);

(h) incubating the infected culture under conditions of about 26-28°C for a predetermined time (page 27; Part X);

This method meets all of the limitations (a)-(h) encompassed by claims 1-11, 13-22, 25-29, and 31-44, except that limitation that the protein used is the soluble RAGE protein. The Clontech manual (page 4) further teaches that proteins in the "baculovirus expression system can express genes from bacteria, viruses, plants, and mammals at levels from 1-500 mg/liter; most proteins are expressed in the 10-100 mg/liter range, although making predictions is difficult". The Clontech manual does not teach using this method with the soluble RAGE protein or purification of the protein using Sepharose.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use soluble RAGE as taught by Morser in the method taught by the Clontech manual, and to purify the soluble RAGE protein from the insect media using Sepharose as Morser teaches. The person of ordinary skill in the art would be motivated to do so because Morser teaches expression of soluble RAGE and its use in use in binding advance glycosylation end-products (AGEs) and a means to purify the protein once it is expressed, and the Clontech manual teaches a general method of high-level expression of any desired protein.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual would work just as well with soluble RAGE as with any other protein, and the method of purification with Sepharose is taught by Morser to work with RAGE. Because the method encompassed by the claims is identical to the Clontech method, and the specification teaches that this method produces over 250 mg/L of RAGE protein, the Clontech method would have been expected to one of ordinary skill in the art to produce over 250 mg/L of RAGE protein.

Claim 47-51, 53, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morser et al, U.S. Patent No. 5,864,018, published 1/26/1999 (cited by the Applicants as Reference #9 on the IDS submitted 9/4/2002) in view of in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002) as applied to claims 1-11, 13-22, 25-29, and 31-44 above, and further in view of Taticek et al, 1997. Biotechnol. Bioeng. 54: 142-152.

Claims 47-51, 53 and 54 encompass a method with all of the limitations of steps (a)-(h) of the method described above, as well as purification of the RAGE protein from the insect media with Sepharose, with the further limitation that the cells are grown to a density of 1.5-2.5x10^6 cells/ml prior to viral infection.

The teachings of Morser regarding expression of the RAGE protein are taught above. Morser does not teach expression of RAGE by a method encompassed by claims 47-51, 53, and 54.

The teachings of the Clontech Manual regarding expression of proteins are summarized above. The Clontech Manual teaches all of the limitations of steps (a)-(h) of the method described above, but does not teach the additional limitation that the infection of the cells after cells are grown to a density of 1.5-2.5 x10^6 cells/ml.

Taticek teaches that dissolved oxygen decreases in cultures soon after infection of Sf21 cells with baculovirus (Figure 4). Taticek further teaches that cells infected at 2-2.4x106 cells/mL (see page 144) and supplemented with dissolved oxygen, glucose and glutamine have increased protein expression of a secreted glycoprotein (see Figure 10, page 149). Taticek does not teach expression of soluble RAGE protein, or a method of expression that meets all of the limitations of steps (a)-(h) described above.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use soluble RAGE as taught by Morser in the method taught by the Clontech manual, and to further modify the method to use the cell density at time of infection as taught by Taticek, and to purify the soluble RAGE protein from the insect media using Sepharose as Morser teaches. The person of ordinary skill in the art would be motivated to do so because Morser teaches expression of soluble RAGE and its use

in use in binding advance glycosylation end-products (AGEs) and a means to purify the protein once it is expressed, and the Clontech manual teaches a general method of high-level expression of any desired protein, and Taticek teaches modifications to culture conditions to increase the protein expression.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual would work just as well with soluble RAGE as with any other protein, and the method of purification with Sepharose is taught by Morser to work with RAGE, and the method of Taticek would work to increase the protein expression of the soluble RAGE protein. Because the method encompassed by the claims is identical to the Clontech method, except that it uses a higher cell density at time of infection, and the specification teaches that a method identical to the Clontech method produces over 250 mg/L of RAGE protein, the person of ordinary skill in the art would reasonably expect that the Clontech method as modified by Taticek would also produce over 250 mg/L of RAGE protein.

Claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neeper et al, 1992 (cited by Applicants as Reference #62 on the IDS submitted 9/4/2002) in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002).

Claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44 encompass a method with steps (a)-(h) described above, except that claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44 are drawn to SEQ ID NO: 1, or sequences substantially homologous, which encompasses sequences up to 75% similar to SEQ ID NO: 1, as described above.

Neeper teaches cloning and expression of a RAGE receptor sequence that is 99.8% identical to instant SEQ ID NO: 1 (see Sequence Alignment #3). Neeper further teaches (Figure 8, page 15003) that this receptor binds AGEs (advanced glycosylation end products). Neeper does not teach expression of the RAGE receptor by a method encompassed by claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44.

The teachings of the Clontech are summarized above. The Clontech manual does not teach expression of a RAGE receptor as taught by Neeper.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use RAGE as taught by Neeper in the method taught by the Clontech manual. The person of ordinary skill in the art would be motivated to do so because Neeper teaches expression of RAGE and its use in use in binding advance glycosylation end-products (AGEs), and the Clontech manual teaches a general method of high-level expression of any desired protein.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual would work just as well with RAGE as with any other protein. Because the method encompassed by the claims is identical to the Clontech method, and the specification teaches that this method produces over 250 mg/L of a RAGE protein substantially homologous to SEQ ID NO: 1, the Clontech method would have been expected to one of ordinary skill in the art to produce over 250 mg/L of RAGE protein of the sequence taught by Neeper.

Claims 7 and 29 are rejected under 35 U.S.C 103(a) as being unpatentable over Neeper et al, 1992 (cited by Applicants as Reference #62 on the IDS submitted 9/4/2002) in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002) as applied to claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44 above, and in further view of Morser et al, U.S. Patent No. 5,864,018, published 1/26/1999 (cited by the Applicants as Reference #9 on the IDS submitted 9/4/2002).

Claims 7 and 29 encompass a method with all of the limitations of steps (a)-(h) of the method described above, with the further limitation that the RAGE protein is purified from the insect media using Sepharose.

The teachings of Neeper and the Clontech Manual regarding this method are summarized above. Neither Neeper nor the Clontech Manual teach purification of the RAGE protein using Sepharose.

Morser teaches (col 21, line 9) purification of a recombinant RAGE protein from insect cell culture media.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use RAGE as taught by Neeper in the method taught by the Clontech manual, and further purify the RAGE protein from the insect media as taught by Morser. The person of ordinary skill in the art would be motivated to do so because Neeper teaches expression of RAGE and its use in use in binding advance glycosylation end-products (AGEs), and the Clontech manual teaches a general method of high-level expression of any desired protein, and Morser teaches how to recover and purify the protein for use following expression.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual and the purification taught by Morser would work just as well with RAGE as with any other protein. Because the method encompassed by the claims is identical to the Clontech method, and the specification teaches that this method produces over 250 mg/L of a RAGE protein substantially homologous to SEQ ID NO: 1, the Clontech method would have been expected to one of ordinary skill in the art to produce over 250 mg/L of RAGE protein of the sequence taught by Neeper.

Claims 47 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neeper et al, 1992 (cited by Applicants as Reference #62 on the IDS submitted 9/4/2002) in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002) as applied to claims 1-6, 8-12, 15-22, 25-28, 30, and 33-44 above, and in further view of Taticek et al (1997. Biotechnol. Bioeng. 54m 142-152).

Claims 47 and 49-52 encompass a method with all of the limitations of steps (a)-(h) of the method described above, with the further limitations that the cells are grown to a density of 1.5-2.5x10^6 cells/ml prior to viral infection, and that the RAGE protein is instant SEQ ID NO: 1, or a sequence substantially homologous thereto.

Neeper et al teaches cloning and expression of a RAGE receptor sequence that is 99.8% identical to instant SEQ ID NO: 1 (see Sequence Alignment #3). Neeper further teaches (Figure 8, page 15003) that this receptor binds AGEs (advanced glycosylation end products). Neeper does not teach expression of the RAGE receptor by a method encompassed by claim 47 and 49-52.

The teachings of the Clontech manual are summarized above. The Clontech manual does not teach expression of a RAGE protein substantially homologous to that encoded by SEQ ID NO: 1, or infection of the cells after cells are grown to a density of 1.5-2.5 $x10^6$ cells/ml.

Taticek teaches that dissolved oxygen decreases in cultures soon after infection of Sf21 cells with baculovirus (Figure 4). Taticek further teaches that cells infected at 2-2.4x106 cells/mL (see page 144) and supplemented with dissolved oxygen, glucose and glutamine have increased protein expression of a secreted glycoprotein (see Figure 10, page 149). Taticek does not teach expression of a RAGE protein substantially homologous to that encoded by SEQ ID NO: 1, or a method of expression that meets all of the limitations of steps (a)-(h) described above.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use the RAGE as taught by Neeper in the method taught by the Clontech manual, and to further modify the method to use the cell density at time of infection as taught by Taticek. The person of ordinary skill in the art would be motivated to do so because Neeper teaches expression of soluble RAGE and its use in use in binding advance glycosylation end-products (AGEs), and the Clontech manual teaches a general method of high-level expression of any desired protein, and Taticek teaches modifications to culture conditions to increase the protein expression.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual would work just as well with the RAGE taught by Neeper as with any other protein, and the method of Taticek would work to increase the protein expression of the RAGE protein. Because the method encompassed by claim 52 is identical to the Clontech method, except that it uses a higher cell density at time of infection, and the specification teaches that a

method identical to the Clontech method produces over 250 mg/L of RAGE protein, the person of ordinary skill in the art would reasonably expect that the Clontech method as modified by Taticek would also produce over 250 mg/L of RAGE protein.

Claims 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Neeper et al, 1992 (cited by Applicants as Reference #62 on the IDS submitted 9/4/2002) in view of the Clontech BacPak Baculovirus Expression System User Manual, published 14 May 1999 (cited by Applicants as Reference #30 on the IDS submitted 9/4/2002) and in further view of Taticek (1997. Biotechnol. Bioeng. 54m 142-152) as applied to claims 47 and 49-52 above, and in further view of Morser et al, U.S. Patent No. 5,864,018, published 1/26/1999 (cited by the Applicants as Reference #9 on the IDS submitted 9/4/2002).

Claim 48 encompasses a method with all of the limitations of steps (a)-(h) of the method described above, with the further limitations that the cells are grown to a density of $1.5\text{-}2.5x10^6$ cells/ml prior to viral infection, and that the RAGE protein is instant SEQ ID NO: 1, or a sequence substantially homologous thereto, and with the further limitation that the RAGE protein is purified from the insect media using Sepharose.

The teachings of Neeper, the Clontech Manual, and Taticek with regard to this method are summarize above. None of these references teach purification of RAGE protein purified from the insect media using Sepharose.

Morser teaches (col 21, line 9) purification of a recombinant RAGE protein from insect cell culture media.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to use the RAGE as taught by Neeper in the method taught by the Clontech manual, and to further modify the method to use the cell density at time of infection as taught by Taticek, and to purify the RAGE protein from the insect media as taught by Morser. The person of ordinary skill in the art would be motivated to do so because Neeper teaches expression of soluble RAGE and its use in use in binding advance glycosylation end-products (AGEs), and the Clontech manual teaches a general method of high-level expression of any desired protein, and Taticek teaches

modifications to culture conditions to increase the protein expression, and Morser teaches how to recover and purify the protein for use following expression.

The person of ordinary skill in the art would have expected success because, in the absence of other evidence, the method taught by Clontech manual and the purification taught by Morser would work just as well with the RAGE taught by Neeper as with any other protein, and the method of Taticek would work to increase the protein expression of the RAGE protein. Because the method encompassed by claim 52 is identical to the Clontech method, except that it uses a higher cell density at time of infection, and the specification teaches that a method identical to the Clontech method produces over 250 mg/L of RAGE protein, the person of ordinary skill in the art would reasonably expect that the Clontech method as modified by Taticek would also produce over 250 mg/L of RAGE protein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

SEQUENCE ALIGNMENT #1

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OM nucleic - nucleic search, using sw model

Run on: March 14, 2005, 17:21:07 ; Search time 197.91 Seconds
(without alignments)
8433.118 Million cell updates/sec

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Perfect score: 1020
Sequence: 1 atggcagccggaacagcagt.....gaggatcagggctggtctag 1020

Scoring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

Searched: 1202784 seqs, 818138359 residues

Total number of hits satisfying chosen parameters: 2405568

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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	2	1015	99.5	1215	4	US-09-949-016-5154	Sequence 5154, Ap
	3	1009.8	99.0	1391	4	US-09-638-649-4	Sequence 4, Appli
	4	1009.8	99.0	1391	4	US-09-638-648-4	Sequence 4, Appli
	5	986.8	96.7	1405	4	US-08-755-235-3	Sequence 3, Appli
	6	945.8	92.7	957	2	US-08-633-148-3	Sequence 3, Appli
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	35	39.2	3.8	6108	4	US-09-949-016-12213	Sequence 12213, A
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	37	38.4	3.8	22218	4	US-09-949-016-14240	Sequence 14240, A
	38	38	3.7	1416	4	US-09-902-540-4687	Sequence 4687, Ap
	39	38	3.7	3991	3	US-08-506-296B-3	Sequence 3, Appli
	40	38	3.7	28558	4	US-09-902-540-1231	Sequence 1231, Ap
c	41	37.6	3.7	510	4	US-09-252-991A-5973	Sequence 5973, Ap
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c	45	37.4	3.7	1707	3	US-09-250-585A-1	Sequence 1, Appli

ALIGNMENTS

RESULT 1
US-08-633-148-1
; Sequence 1, Application US/08633148
; Patent No. 5864018
; GENERAL INFORMATION:
; APPLICANT: MORSER, MICHAEL J.
; APPLICANT: NAGASHIMA, MARIKO
; APPLICANT: HOLLANDER, DORIS A.
; TITLE OF INVENTION: ANTIBODIES TO ADVANCED GLYCOSYLATION
; TITLE OF INVENTION: END-PRODUCT RECEPTOR POLYPEPTIDES AND USES THEREFOR
; NUMBER OF SEQUENCES: 23
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: TOWNSEND & TOWNSENT & CREW LLP
; STREET: TWO EMBARCADERO CENTER, 8TH FLOOR
; CITY: SAN FRANCISCO
; STATE: CALIFORNIA
; COUNTRY: U.S.A.
; ZIP: 94111
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.30
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/633,148
; FILING DATE: 16-APR-1996
; CLASSIFICATION: 435
; ATTORNEY/AGENT INFORMATION:
; NAME: MURPHY ESQ., MATTHEW B.
; REGISTRATION NUMBER: 39,787
; REFERENCE/DOCKET NUMBER: 014618-005600US
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (415) 326-2400
; TELEFAX: (415) 326-2422
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 1023 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: linear
; MOLECULE TYPE: DNA (genomic)
US-08-633-148-1

Query Match 99.5%; Score 1015; DB 2; Length 1023;
Best Local Similarity 100.0%; Pred. No. 6e-271;
Matches 1015; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 ATGGCAGCCGGAACAGCAGTTGGAGCCTGGGTGCTGGTCCTCAGTCTGTGGGGGGCAGTA 60
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Qy         181 TGGAAGGTCCTGTCTCCCCAGGGAGGAGGCCCCTGGGACAGTGTGGCTCGTGTCCTTCCC 240
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Qy         361 CCTGGGAAGCCAGAAATTGTAGATTCTGCCTCTGAACTCACGGCTGGTGTTCCCAATAAG 420
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Qy         661 CGCACAGCCCCCATCCAGCCCCGTGTCTGGGAGCCTGTGCCTCTGGAGGAGGTCCAATTG 720
Db         661 CGCACAGCCCCCATCCAGCCCCGTGTCTGGGAGCCTGTGCCTCTGGAGGAGGTCCAATTG 720

Qy         721 GTGGTGGAGCCAGAAGGTGGAGCAGTAGCTCCTGGTGGAACCGTAACCCTGACCTGTGAA 780
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Qy         781 GTCCCTGCCCAGCCCTCTCCTCAAATCCACTGGATGAAGGATGGTGTGCCCTTGCCCCTT 840
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Qy         841 CCCCCCAGCCCTGTGCTGATCCTCCCTGAGATAGGGCCTCAGGACCAGGGAACCTACAGC 900
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Qy         961 ATCGAACCAGGCGAGGAGGGGCCAACTGCAGGCTCTGTGGGAGGATCAGGGCTGG 1015
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RESULT 2
US-09-949-016-5154
; Sequence 5154, Application US/09949016
; Patent No. 6812339
; GENERAL INFORMATION:
;  APPLICANT: VENTER, J. Craig et al.
;  TITLE OF INVENTION: POLYMORPHISMS IN KNOWN GENES ASSOCIATED
;  TITLE OF INVENTION:  WITH HUMAN DISEASE, METHODS OF DETECTION AND USES THEREOF
;  FILE REFERENCE: CL001307
;  CURRENT APPLICATION NUMBER: US/09/949,016
;  CURRENT FILING DATE:  2000-04-14
;  PRIOR APPLICATION NUMBER: 60/241,755
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 60/237,768
;  PRIOR FILING DATE: 2000-10-03
;  PRIOR APPLICATION NUMBER: 60/231,498
;  PRIOR FILING DATE: 2000-09-08
;  NUMBER OF SEQ ID NOS: 207012
;  SOFTWARE: PastSEQ for Windows Version 4.0
; SEQ ID NO 5154
;   LENGTH: 1215
;   TYPE: DNA
;   ORGANISM: Human
US-09-949-016-5154

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  Best Local Similarity  100.0%;  Pred. No. 6.8e-271;
  Matches 1015;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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SEQUENCE ALIGNMENT #2

GenCore version 5.1.6
Copyright (c) 1993 - 2005 Compugen Ltd.

OM nucleic - nucleic search, using sw model

Run on: March 14, 2005, 17:21:07 ; Search time 65.194 Seconds
(without alignments)
8433.118 Million cell updates/sec

Title: US-10-091-019-4
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Scoring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

Searched: 1202784 seqs, 818138359 residues

Total number of hits satisfying chosen parameters: 2405568

Minimum DB seq length: 0
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Post-processing: Minimum Match 0%
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Listing first 45 summaries

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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	2	336	100.0	1215	4	US-09-949-016-5154	Sequence 5154, Ap
	3	332.8	99.0	957	2	US-08-633-148-3	Sequence 3, Appli
	4	332.8	99.0	1391	4	US-09-638-649-4	Sequence 4, Appli
	5	332.8	99.0	1391	4	US-09-638-648-4	Sequence 4, Appli
	6	332.8	99.0	1405	4	US-08-755-235-3	Sequence 3, Appli
	7	270.6	80.5	1426	4	US-09-638-649-2	Sequence 2, Appli
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	9	270.6	80.5	1438	4	US-08-755-235-1	Sequence 1, Appli
	10	239	71.1	1347	4	US-09-638-648-6	Sequence 6, Appli
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c	21	33.6	10.0	1239	4	US-09-949-016-1713	Sequence 1713, Ap
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	37	32	9.5	3192	4	US-09-388-995-2	Sequence 2, Appli
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c	41	31.4	9.3	4418	4	US-09-064-199-13	Sequence 13, Appl
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c	45	31.4	9.3	4543	2	US-08-519-547A-5	Sequence 5, Appli

ALIGNMENTS

RESULT 1
US-08-633-148-1
; Sequence 1, Application US/08633148
; Patent No. 5864018
; GENERAL INFORMATION:
; APPLICANT: MORSER, MICHAEL J.
; APPLICANT: NAGASHIMA, MARIKO
; APPLICANT: HOLLANDER, DORIS A.
; TITLE OF INVENTION: ANTIBODIES TO ADVANCED GLYCOSYLATION
; TITLE OF INVENTION: END-PRODUCT RECEPTOR POLYPEPTIDES AND USES THEREFOR
; NUMBER OF SEQUENCES: 23
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: TOWNSEND & TOWNSENT & CREW LLP
; STREET: TWO EMBARCADERO CENTER, 8TH FLOOR
; CITY: SAN FRANCISCO
; STATE: CALIFORNIA
; COUNTRY: U.S.A.
; ZIP: 94111
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.30
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/633,148
; FILING DATE: 16-APR-1996
; CLASSIFICATION: 435
; ATTORNEY/AGENT INFORMATION:
; NAME: MURPHY ESQ., MATTHEW B.
; REGISTRATION NUMBER: 39,787
; REFERENCE/DOCKET NUMBER: 014618-005600US
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (415) 326-2400
; TELEFAX: (415) 326-2422
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 1023 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: linear
; MOLECULE TYPE: DNA (genomic)
US-08-633-148-1

Query Match 100.0%; Score 336; DB 2; Length 1023;
Best Local Similarity 100.0%; Pred. No. 1e-93;
Matches 336; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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RESULT 2
US-09-949-016-5154
; Sequence 5154, Application US/09949016
; Patent No. 6812339
; GENERAL INFORMATION:
;  APPLICANT: VENTER, J. Craig et al.
;  TITLE OF INVENTION: POLYMORPHISMS IN KNOWN GENES ASSOCIATED
;  TITLE OF INVENTION:  WITH HUMAN DISEASE, METHODS OF DETECTION AND USES THEREOF
;  FILE REFERENCE:. CL001307
;  CURRENT APPLICATION NUMBER: US/09/949,016
;  CURRENT FILING DATE:  2000-04-14
;  PRIOR APPLICATION NUMBER: 60/241,755
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 60/237,768
;  PRIOR FILING DATE: 2000-10-03
;  PRIOR APPLICATION NUMBER: 60/231,498
;  PRIOR FILING DATE: 2000-09-08
;  NUMBER OF SEQ ID NOS: 207012
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 5154
;   LENGTH: 1215
;   TYPE: DNA
;   ORGANISM: Human
US-09-949-016-5154

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  Matches  336;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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RESULT 3
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; Sequence 3, Application US/08633148
; Patent No. 5864018
;  GENERAL INFORMATION:
;    APPLICANT:  MORSER, MICHAEL J.
;    APPLICANT:  NAGASHIMA, MARIKO
;    APPLICANT:  HOLLANDER, DORIS A.
;    TITLE OF INVENTION:  ANTIBODIES TO ADVANCED GLYCOSYLATION
;    TITLE OF INVENTION:  END-PRODUCT RECEPTOR POLYPEPTIDES AND USES THEREFOR
;    NUMBER OF SEQUENCES:  23
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  TOWNSEND & TOWNSENT & CREW LLP
;      STREET:  TWO EMBARCADERO CENTER, 8TH FLOOR
;      CITY:  SAN FRANCISCO
;      STATE:  CALIFORNIA
;      COUNTRY:  U.S.A.
;      ZIP:  94111
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/633,148
;      FILING DATE:  16-APR-1996
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  MURPHY ESQ., MATTHEW B.
;      REGISTRATION NUMBER:  33,787
;      REFERENCE/DOCKET NUMBER:  014618-005600US
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (415) 326-2400
;      TELEFAX:  (415) 326-2422
;  INFORMATION FOR SEQ ID NO:  3
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  957 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  DNA (genomic)
US-08-633-148-3

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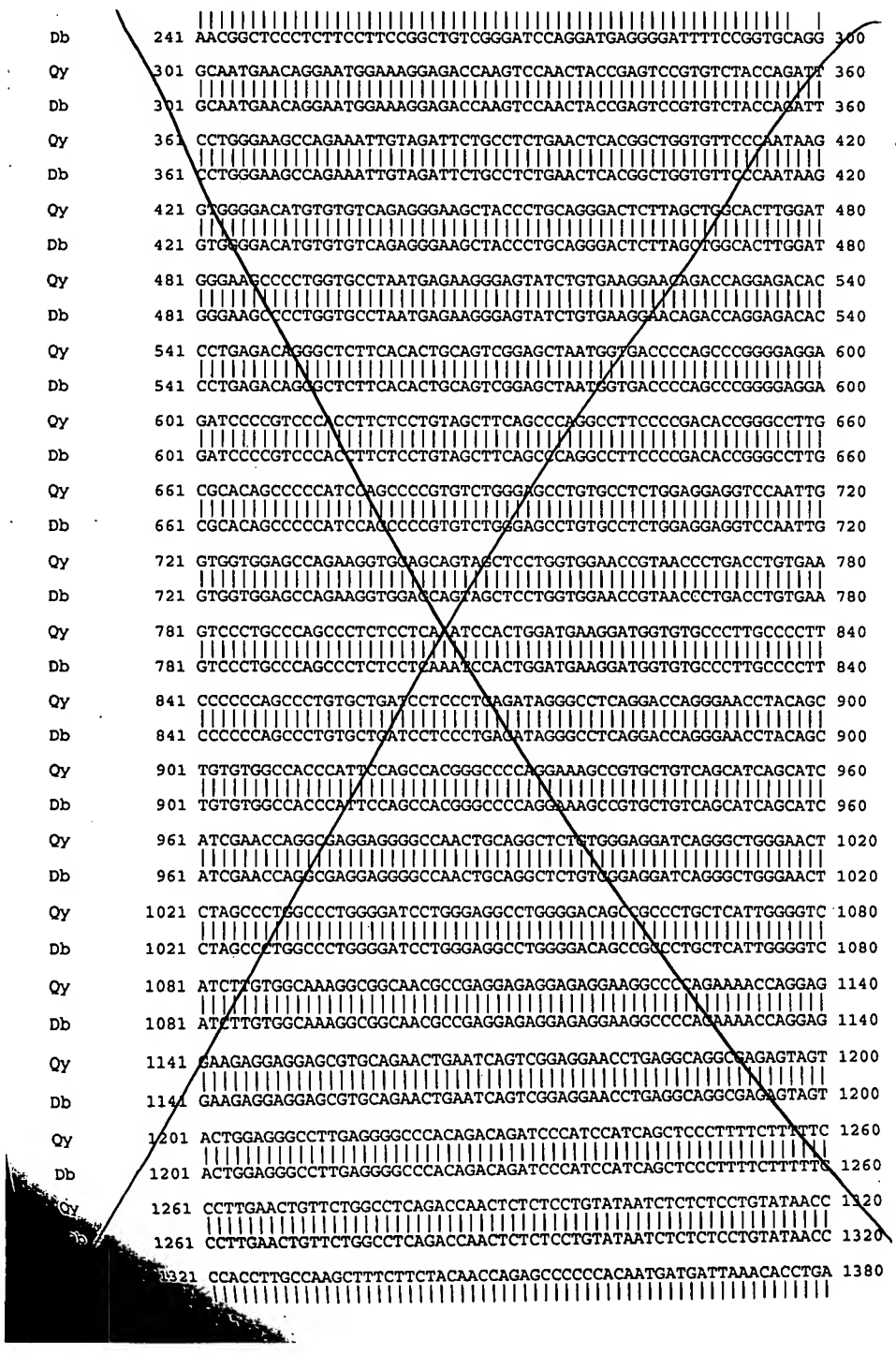

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Db 1381 CACATCTTGCA 1391

RESULT 2
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LOCUS HUMRAGE 1391 bp mRNA linear PRI 09-DEC-1993
DEFINITION Human receptor for advanced glycosylation end products (RAGE) mRNA, partial cds.
ACCESSION M91211
VERSION M91211.1 GI:190845
KEYWORDS RAGE; cell surface receptor.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 1391)
AUTHORS Neeper,M., Schmidt,A.M., Brett,J., Yan,S.D., Wang,F., Pan,Y.C., Elliston,K., Stern,D. and Shaw,A.
TITLE Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins
JOURNAL J. Biol. Chem. 267 (21), 14998-15004 (1992)
MEDLINE 92340547
PUBMED 1378843
REFERENCE 2 (bases 1 to 1391)
AUTHORS Shaw,A.
TITLE Direct Submission
JOURNAL Submitted (15-APR-1992) A. Shaw, Department of Cellular and Molecular Biology, Merck Sharp and Dohme Research Laboratories, West Point, PA 19486 USA
COMMENT Original source text: Homo sapiens cDNA to mRNA.
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/db_xref="GI:190846"
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polyA_site 1391
ORIGIN

Query Match 99.8%; Score 1387.8; DB 9; Length 1391;
Best Local Similarity 99.9%; Pred. No. 0;
Matches 1389; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

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Db 61 GTAGGTGCTCAAAACATCACAGCCCGGATTGGCGAGCCACTGGTGCTGAAGTGTAAGGGG 120
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Qy        241 AACGGCTCCCTCTTCCTTCCGGCTGTCGGGATCCAGGATGAGGGGATTTTCCGGTGCCAG 300
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Qy        301 GCAATGAACAGGAATGGAAAGGAGACCAAGTCCAACTACCGAGTCCGTGTCTACCAGATT 360
Db        301 GCAATGAACAGGAATGGAAAGGAGACCAAGTCCAACTACCGAGTCCGTGTCTACCAGATT 360
Qy        361 CCTGGGAAGCCAGAAATTGTAGATTCTGCCTCTGAACTCACGGCTGGTGTTCCCAATAAG 420
Db        361 CCTGGGAAGCCAGAAATTGTAGATTCTGCCTCTGAACTCACGGCTGGTGTTCCCAATAAG 420
Qy        421 GTGGGGACATGTGTGTCAGAGGGAAGCTACCCTGCAGGGACTCTTAGCTGGCACTTGGAT 480
Db        421 GTGGGGACATGTGTGTCAGAGGGAAGCTACCCTGCAGGGACTCTTAGCTGGCACTTGGAT 480
Qy        481 GGGAAGCCCCTGGTGCCTAATGAGAAGGGAGTATCTGTGAAGGAACAGACCAGGAGACAC 540
Db        481 GGGAAGCCCCTGGTGCCTAATGAGAAGGGAGTATCTGTGAAGGAACAGACCAGGAGACAC 540
Qy        541 CCTGAGACAGGGCTCTTCACACTGCAGTCGGAGCTAATGGTGACCCCAGCCCGGGGAGGA 600
Db        541 CCTGAGACAGGGCTCTTCACACTGCAGTCGGAGCTAATGGTGACCCCAGCCCGGGGAGGA 600
Qy        601 GATCCCCGTCCCACCTTCTCCTGTAGCTTCAGCCCAGGCCTTCCCCGACACCGGGCCTTG 660
Db        601 GATCCCCGTCCCACCTTCTCCTGTAGCTTCAGCCCAGGCCTTCCCCGACACCGGGCCTTG 660
Qy        661 CGCACAGCCCCCATCCAGCCCCGTGTCTGGGAGCCTGTGCCTCTGGAGGAGGTCCAATTG 720
Db        661 CGCACAGCCCCCATCCAGCCCCGTGTCTGGGAGCCTGTGCCTCTGGAGGAGGTCCAATTG 720
Qy        721 GTGGTGGAGCCAGAAGGTGGAGCAGTAGCTCCTGGTGGAACCGTAACCCTGACCTGTGAA 780
Db        721 GTGGTGGAGCCAGAAGGTGGAGCAGTAGCTCCTGGTGGAACCGTAACCCTGACCTGTGAA 780
Qy        781 GTCCCTGCCCAGCCCTCTCCTCAAATCCACTGGATGAAGGATGGTGTGCCCTTGCCCCTT 840
Db        781 GTCCCTGCCCAGCCCTCTCCTCAAATCCACTGGATGAAGGATGGTGTGCCCTTGCCCCTT 840
Qy        841 CCCCCCAGCCCTGTGCTGATCCTCCCTGAGATAGGGCCTCAGGACCAGGGAACCTACAGC 900
Db        841 CCCCCCAGCCCTGTGCTGATCCTCCCTGAGATAGGGCCTCAGGACCAGGGAACCTACAGC 900
Qy        901 TGTGTGGCCACCCATTCCAGCCACGGGCCCCAGGAAAGCCGTGCTGTCAGCATCAGCATC 960
Db        901 TGTGTGGCCACCCATTCCAGCCACGGGCCCCAGGAAAGCCGTGCTGTCAGCATCAGCATC 960
Qy        961 ATCGAACCAGGCGAGGAGGGGCCAACTGCAGGCTCTGTGGGAGGATCAGGGCTGGGAACT 1020
Db        961 ATCGAACCAGGCGAGGAGGGGCCAACTGCAGGCTCTGTGGGAGGATCAGGGCTGGGAACT 1020
Qy       1021 CTAGCCCTGGCCCTGGGGATCCTGGGAGGCCTGGGGACAGCCGCCCTGCTCATTGGGGTC 1080
Db       1021 CTAGCCCTGGCCCTGGGGATCCTGGGAGGCCTGGGGACAGCCGCCCTGCTCATTGGGGTC 1080
Qy       1081 ATCTTGTGGCAAAGGCGGCAACGCCGAGGAGAGGAGAGGAAGGCCCCAGAAAACCAGGAG 1140
Db       1081 ATCTTGTGGCAAAGGCGGCAACGCCGAGGAGAGGAGAGGAAGGCCCCAGAAAACCAGGAG 1140
Qy       1141 GAAGAGGAGGAGCGTGCAGAACTGAATCAGTCGGAGGAACCTGAGGCAGGCGAGAGTAGT 1200
Db       1141 GAAGAGGAGGAGCGTGCAGAACTGAATCAGTCGGAGGAACCTGAGGCAGGCGAGAGTAGT 1200
Qy       1201 ACTGGAGGGCCTTGAGGGGCCCACAGACAGATCCCATCCATCAGCTCCCTTTTCTTTTTC 1260
Db       1201 ACTGGAGGGCCTTGAGGGGCCCACAGACAGATCCCATCCATCAGCTCCCTTTTCTTTTTC 1260
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Qy       1261 CCTTGAACTGTTCTGGCCTCAGACCAACTCTCTCCTGTATAATCTCTCTCCTGTATAACC 1320
Db       1261 CCTTGAACTGTTCTGGCCTCAGACCAACTCTCTCCTGTATAATCTCTCTCCTGTATAACC 1320
Qy       1321 CCACCTTGCCAAGCTTTCTTCTACAACCAGAGCCCCCCACAATGATGATTAAACACCTGA 1380
Db       1321 CCACCTTGCCAAGCTTTCTTCTACAACCAGAGCCCCCCACAATGATGATTAAACACCTGA 1380
Qy       1381 CACATCTTGCA 1391
Db       1381 CACATCTTGCA 1391
```

RESULT 3
BC020669

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LOCUS       BC020669                1436 bp    mRNA    linear   PRI 29-JUN-2004
DEFINITION  Homo sapiens advanced glycosylation end product-specific receptor,
            transcript variant 1, mRNA (cDNA clone MGC:22357 IMAGE:4718076)
            complete cds.
ACCESSION   BC020669
VERSION     BC020669.1  GI:18088362
KEYWORDS    MGC.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1436)
  AUTHORS   Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
            Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
            Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
            Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F.,
            Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L.,
            Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
            Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S.,
            Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J.,
            Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J.,
            McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
            Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W.,
            Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A.,
            Fahey,J., Helton,E., Ketteman,M., Madan,A., Rodrigues,S.,
            Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
            Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
            Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M.,
            Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
            Schnerch,A., Schein,J.E., Jones,S.J. and Marra,M.A.
  TITLE     Generation and initial analysis of more than 15,000 full-length
            human and mouse cDNA sequences
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
   PUBMED   12477932
REFERENCE   2  (bases 1 to 1436)
  AUTHORS   Strausberg,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JAN-2002) National Institutes of Health, Mammalian
            Gene Collection (MGC), Cancer Genomics Office, National Cancer
            Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590,
            USA
  REMARK    NIH-MGC Project URL: http://mgc.nci.nih.gov
COMMENT     Contact: MGC help desk
            Email: cgapbs-r@mail.nih.gov
            Tissue Procurement: CLONTECH
            cDNA Library Preparation: CLONTECH Laboratories, Inc.
            cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
            DNA Sequencing by: Sequencing Group at the Stanford Human Genome
            Center, Stanford University School of Medicine, Stanford, CA  94305
            Web site:       http://www-shgc.stanford.edu
            Contact:  (Dickson, Mark) mcd@paxil.stanford.edu
            Dickson, M., Schmutz, J., Grimwood, J., Rodriquez, A., and Myers,
            R. M.

            Clone distribution: MGC clone distribution information can be found
            through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
            Series: IRAL Plate: 37 Row: e Column: 17
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